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Problems on Quantitative Genetics

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QUANTITATIVE GENETICS

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PREFACE

These problems have been prepared specifically for use with *Introduction to Quantitative Genetics* (2nd edn). Though most of the problems will be intelligible without reference to the book, many of the solutions will not be easy to follow without it because frequent reference is made to the numbered equations and occasionally to some of the Figures. The problems are arranged in order of the chapters in the book, and there is a problem on all the main points in each chapter. Some of the problems are based on the data and solutions of earlier problems. Students are therefore advised to keep their working and solutions for later use; this will save the repetition of calculations. The problems are of varied difficulty, the more difficult ones being mainly toward the end of each chapter. I hope that all students will find some that they can solve immediately and some also that will tax their ingenuity to the full.

When problems are based on imaginary data the arithmetic can be made easy but the exercise tends to be dull. So I have based the problems on real data wherever I could in order to make them more interesting and more realistic. In consequence, however, the arithmetic seldom works out simply and a pocket calculator will be needed for most of the problems.

The solutions given contain fairly full explanations of how the problems are solved and give all the main steps in the calculations. Standard statistical procedures, however, are not fully explained. The statistical calculations required are χ^2 tests of 'goodness of fit'; mean, variance and standard error of the mean; correlation and regression coefficients; analysis of variance. I have tried to ensure that there are no rounding errors in the solutions, and the steps in the calculations are given with as many decimal places as are needed for this purpose. Sampling errors in the data have for the most part been ignored and the solutions are sometimes given with more precision than is justified by the data.

I am very greatly indebted to Dr W. G. Hill for many suggestions about the problems and their solutions; his advice has been invaluable. I am very grateful also to Dr Paul M. Sharp for many helpful suggestions and for checking all the solutions; to Professor N. W. Simmonds for comments on the problems concerning plants; and to many other colleagues for suggestions, particularly about sources of suitable data. The responsibility for any errors that remain is

nine alone. I should be greatful to readers if they will tell me of any errors that hey find.

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April, 1982

CONTENTS

I GENETIC CONSTITUTION OF A POPULATION

1.1 The following numbers of the human M-N blood groups were recorded in a sample of American Whites.

M	MN	N
1787	3039	1303

(1) What are the genotype frequencies observed in this sample?
(2) What are the gene frequencies?
(3) With the gene frequencies observed, what are the genotype frequencies expected from the Hardy–Weinberg law?
(4) How well do the observed frequencies agree with the expectation?

Data from Wiener, A. S. (1943) quoted by Stern, C. (1973) *Principles of Human Genetics*. Freeman, San Francisco.

[Solution 1]

1.2 About 30 per cent of people do not recognize the bitter taste of phenyl-thio-carbamate (PTC). Inability to taste it is due to a single autosomal recessive gene. What is the frequency of the non-tasting gene, assuming the population to be in Hardy–Weinberg equilibrium?

[Solution 11]

1.3 Albinism occurs with a frequency of about 1 in 20,000 in European populations. Assuming it to be due to a single autosomal recessive gene, and assuming the population to be in Hardy–Weinberg equilibrium, what proportion of people are carriers? Only an approximate answer is needed.

[Solution 21]

1.4 As an exercise in algebra, work out the gene frequency of a recessive mutant in a random-breeding population that would result in one third of normal individuals being carriers.

[Solution 31]

1.5 Three allelic variants, A, B, and C, of the red cell acid phosphatase enzyme were found in a sample of 178 English people. All genotypes are distinguishable by electrophoresis, and the frequencies in the sample were

Genotype	AA	AB	BB	AC	BC	CC
Frequency (%)	9.6	48.3	34.3	2.8	5.0	0.0

What are the gene frequencies in the sample? Why were no CC individuals found?

Data from Spencer, N., *et al.* (1964) *Nature*, **201**, 299–300.

[Solution 41]

1.6 About 7 per cent of men are colour-blind in consequence of a sex-linked recessive gene. Assuming Hardy–Weinberg equilibrium, what proportion of women are expected to be (1) carriers, and (2) colour-blind? (3) In what proportion of marriages are both husband and wife expected to be colour-blind?

[Solution 51]

1.7 Sine oculis (*so*) and cinnabar (*cn*) are two autosomal recessive genes in *Drosophila melanogaster*. They are very closely linked and can be treated as if they were alleles at one locus. The 'heterozygote', *so/cn*, is wild-type and is distinguishable from both homozygotes; (*so/so* has no eyes; *cn/cn* has white eyes if the stock is made homozygous for another eye-colour mutant, brown, *bw*). In a class experiment 4 males and 4 females of an *so/so* stock were put in a vial together with 16 males and 16 females from a *cn/cn* stock and allowed to mate. There were 20 such vials. The total count of progeny, classified by genotype, was as follows.

so/so	*so/cn*	*cn/cn*
135	359	947

How do these numbers differ from the Hardy–Weinberg expectations? Suggest a reason for the discrepancy.

[Solution 61]

1.8 Suppose that *Drosphila* cultures are set up in vials as described in Problem 1.7, but this time with a gene frequency of 0.5. This is done by putting 10 males and 10 females of each stock in each vial. The supply of *so/so* females ran out and only 4 were left for the last vial. So, to preserve the intended gene frequency and numbers of parents, this vial was made up as follows: 16♂♂ + 4♀♀ of *so/so* with 4♂♂ + 16♀♀ of *cn/cn*. The student who got this vial was a bit surprised by what he found. What genotype frequencies would you expect in the progeny?

[Solution 71]

1.9 Prove that when there are any number of alleles at a locus the total frequency of heterozygotes is greatest when all alleles have the same frequency. What is then the total frequency of heterozygotes?

[Solution 81]

1.10 Suppose that a strain of genotype AA BB is mixed with another strain of genotype aa bb, with equal numbers of the two strains and equal numbers of males and females, which mate at random. Call this generation of parents and their progeny generation 0. Subsequent generations also mate at random and there are no differences of fertility or viability among the genotypes. What will be the frequency of the genotype AA bb in the generation 2 progeny if the two loci are (1) unlinked, (2) linked with a recombination frequency of 20 per cent?

[Solution 91]

1.11 How will the solutions of Problem 1.10 be altered if the two strains are crossed by taking males of one strain and females of the other?

[Solution 101]

2 CHANGES OF GENE FREQUENCY

2.1 Rare white-flowered plants occur in populations of a *Delphinium* species which normally has deep blue flowers. In an area in the Rocky Mountains the frequency of white-flowered plants was 7.4×10^{-4}. White-flowered plants were found to set an average of 143 seeds per plant while blue-flowered plants set 229, the reduction in seed-production being due to discrimination by pollinators, which are bumblebees and humming birds. On the assumption that white flowers are due to a single recessive gene, and that the population was in equilibrium, what rate of mutation would be needed to balance the selection?

Data from Waser, N. M. & Price, M. V. (1981) *Evolution*, **35**, 376–90.

[Solution 12]

2.2 If the white flowers in Problem 2.1 were due to a completely dominant gene, which is less likely, what would be the mutation rate needed to maintain equilibrium?

[Solution 22]

2.3 If an allele, *A*, mutates to *a* with a frequency of 1 in 10,000 and back-mutates with a frequency 1 in 100,000, and if the three genotypes have equal fitnesses, what will be the genotype frequencies at equilibrium in a random-mating population?

[Solution 32]

2.4 Refer to Problem 2.3. What would be the consequences of doubling the mutation rate in both directions?

[Solution 42]

2.5 Medical treatment is, or will be, available for several serious autosomal recessive diseases. What would be the long-term consequences if treatment allowed sufferers from such a disease to have on average half the number of children that normal people have, whereas without treatment they would have no children? Assume that the present frequency is the mutation versus selection equilibrium, that in the longterm a new equilibrium will be reached, and that no other circumstances change.

[Solution 52]

2.6 Cystic fibrosis is an autosomal recessive human disease with an incidence of about 1 in 2,500 live births among Caucasians. What would be the consequence in the immediately following generation if the mutation rate were doubled? Assume that the present frequency is the mutation versus selection equilibrium, that back-mutation is negligible, and that affected individuals have no children. Express your result as a percentage increase of incidence and as the number of additional cases per million births.

[Solution 62]

2.7 A careless *Drosophila* stock-keeper allows a stock of a dominant autosomal mutant to be contaminated by wild-type flies. Originally all flies were homozygous for the mutant, but after 10 generations some wild-type flies were found in the stock. Precautions were then taken to prevent further contamination. Suppose that we make the following assumptions: (i) In every generation 1 per cent of flies were contaminants, (ii) all contaminants were homozygous wild-type, (iii) mutant and wild-type flies have equal fitness. With these assumptions what would be (1) the proportion of wild-type flies in the generations after the last contamination, and (2) the proportion of heterozygotes among the flies with the mutant phenotype?

[Solution 72]

2.8 The two closely linked recessive genes of *Drosophila* described in Problem 1.7 can be treated as alleles. Two populations were set up with initial gene frequencies of *so* of 0.2 in one and 0.8 in the other. After 7 generations of random breeding the gene frequency of *so* was close to 0.35 in both populations. What does this tell us about the selection operating?

[Solution 82]

2.9 The gene that makes wild rats resistant to the anticoagulant poison warfarin exhibits heterozygote advantage because rats homozygous for the resistance gene suffer from vitamin K deficiency. Heterozygotes are resistant to the poison and do not suffer from vitamin K deficiency. The proportion of resistant homozygotes that die from vitamin K deficiency was estimated to be 63 per cent. Susceptible homozygotes are not all killed when poison is applied to an area. A population under continuous treatment with poison came to equilibrium with the resistance gene at a frequency of 0.34. What percentage of all rats in this population will die in consequence of the resistance gene and the poisoning.

Data from Greaves, J. H., *et al.* (1977) *Genet. Res.* **30**, 257–63.

[Solution 92]

2.10 Suppose that two mutant genes are used in a class experiment on selection in *Drosophila*. In both cases heterozygotes are distinguishable from homozygotes but the genes are recessive with respect to fitness. (These are not known genes.) With gene (a) mutant homozygotes of both sexes have their fertility reduced by 50 per cent relative to the other genotypes, but have unimpaired viability. With gene (b) mutant homozygotes are fully fertile but both sexes have their pre-adult mortality increased by 50 per cent relative to the other genotypes. In both cases a parental population is made up of 30♂♂ + 30♀♀ homozygous wild-type and 20♂♂ + 20♀♀ homozygous mutant. What genotype frequencies will be found in the progeny? How do they compare with Hardy–Weinberg expectations based on the observed gene frequency in the progeny? What conclusions about the selection can be drawn from the frequencies in the progeny? Why does Δq differ in the two cases?

[Solution 102]

2.11 Derive an expression for the change of gene frequency, Δq, resulting from one generation of selection against a sex-linked recessive lethal gene. Assume that the population before selection has Hardy–Weinberg genotype frequencies and equal gene frequencies in males and females.

[Solution 112]

2.12 What is the approximate equilibrium gene frequency of a deleterious sex-linked recessive gene, when selection is balanced by a mutation rate of u? Human X-linked muscular dystrophy was found in a survey in England to have an incidence of 32.6 per 100,000 males. The mutation rate was estimated from the number of 'sporadic' cases to be 10.5×10^{-5}. Do these estimates agree with the expectation for a population in equilibrium when sufferers from the disease do not reproduce and carriers have normal survival and fertility?

Data from Gardner–Medwin, D. (1970) *J. Med. Genet.*, 7, 334–7.

[Solution 122]

2.13 Red coat colour in many breeds of cattle is due to an autosomal recessive gene, the dominant phenotype being black. Suppose that 1 per cent of red calves are born in a predominantly black breed, and suppose that it is desired to eliminate the red gene. Assuming the genotypes in the initial population to be in Hardy–Weinberg proportions, what proportion of red calves would there be after applying the following alternative selection procedures over two generations? (1) No red animals are used for breeding. (2) In addition to culling all red animals, all black bulls to be used for breeding are first tested by 6 progeny each from cows known to be heterozygotes. Any bull producing one or more red calves in the test is discarded. Cows used for breeding are not tested.

[Solution 132]

3 SMALL POPULATIONS: I. Changes of gene frequency under simplified conditions

In working the problems on Chapter 3, treat the populations as if they were idealized populations.

3.1 Cod fish have two forms of haemoglobin determined by alleles *a* and *b* at one locus. A sample of cod taken off the Norwegian coast had the following frequencies of the three genotypes.

aa	*ab*	*bb*	Total
130	763	1698	2591

Are these frequencies compatible with the sample having been drawn from a random-breeding population? What do they suggest about the breeding structure of the population?

Data from Møller, D. (1968) *Hereditas*, **60**, 1–32.

[Solution 3]

3.2 Among the cod described in Problem 3.1 two distinct races can be recognized by anatomical differences in the otoliths. When the sample was separated into the two races, called 'Arctic' and 'Coastal', the following numbers were found.

	aa	*ab*	*bb*	Total
Arctic	23	250	946	1219
Coastal	107	513	752	1372

What further light does this throw on the question in Problem 3.1?

[Solution 13]

3.3 If a population is maintained by random mating among 20 pairs of parents in every generation, what will be its inbreeding coefficient after 5 and after 10 generations?

[Solution 23]

3.4 Suppose that for a class experiment each student was given 10 pairs of unmated *Drosophila* taken at random from a large stock in which an electrophoretic variant was present at a gene frequency of 0.3. Each student then maintained his sub-population by taking 10 pairs at random to be parents of the next generation. After 5 generations each student determined the gene frequency in his own population by electrophoresis of a sample of 20 flies from the progeny. What would be the average gene frequency found? How much variation would you expect to find among the students in their estimated gene frequencies, assuming that all read their gels correctly?

[Solution 33]

3.5 If the numbers of the three genotypes counted by the students in the experiment of Problem 3.4 were put together, what would be the overall frequencies of the genotypes?

[Solution 43]

3.6 A stock of mice consisted of 18 lines all derived from the same base population but bred separately thereafter. The stock was polymorphic for an autosomal enzyme locus, *Got-1*, with two alleles, *a* and *b*. After 27 generations mice from all the lines were typed by electrophoresis for the genotypes at this locus and the following numbers were found.

aa	*ab*	*bb*	Total
42	76	448	566

What is the inbreeding coefficient indicated by these numbers?

Data from Garnett, I. (1973) *Ph.D. Thesis*. University of Edinburgh.

[Solution 53]

3.7 Suppose that a random-breeding population is sampled and the following genotype frequencies of a protein variant are found.

aa	*ab*	*bb*
0.34	0.52	0.14

(1) Ignoring the question of significance, do these frequencies give evidence of some form of selection operating on the genotypes? (2) How would the conclusion be altered by the knowledge that the individuals in the sample were the progeny of 4 pairs of parents?

[Solution 63]

3.8 Modify equation [3.16] so as to be applicable when there are different numbers of male and female parents, as is usually the case with domestic livestock.

[Solution 73]

4 SMALL POPULATIONS: II. Less simplified conditions

4.1 Suppose that four *Drosophila* stocks are maintained by putting a fixed number of unmated adults in a bottle and allowing them to mate at random. All stocks have 10 female parents but different numbers of male parents, the numbers of males being 10, 5, 2 and 1 respectively. Calculate the effective population size of each stock and the inbreeding coefficient after 10 generations. Assume that there are no differences of fertility among females or among males.

[Solution 83]

4.2 The sex ratio among breeding individuals can be expressed as the number of females per male. Modify equation [4.4] so as to express N_e in terms of the number of females, N_f, and the number of females per male, d.

[Solution 93]

4.3 Suppose that an isolated natural population goes through a regular 5-year cycle of numbers, with the numbers of breeding pairs in successive generations being 500, 50, 100, 200, 400. What is the effective population size and the rate of inbreeding?

[Solution 103]

4.4 Compare the (approximate) rates of inbreeding in two varieties of a plant, one of which is self-fertile and the other self-sterile, when both are propagated by random pollination among 20 individual plants.

[Solution 113]

4.5 It is planned to keep a mouse stock with 8 pair-matings per generation and minimal inbreeding. The plan, however, cannot be strictly adhered to because some pairs fail to provide the two offspring required. In one particular generation the 8 matings provided the following numbers of offspring that were used as parents: 0, 1, 1, 2, 2, 3, 3, 4. What was the effective population size in this generation?

[Solution 123]

4.6 The breeding plan for each of the lines of the mouse stock described in Problem 3.6 was to mate 8 pairs and to use 2 offspring from each pair as parents of the next generation. If this plan had been strictly adhered to, what would have been the effective population size of the lines? What was actually the effective population size indicated by the data in Problem 3.6?

[Solution 133]

5 SMALL POPULATIONS: III. Pedigreed populations and close inbreeding

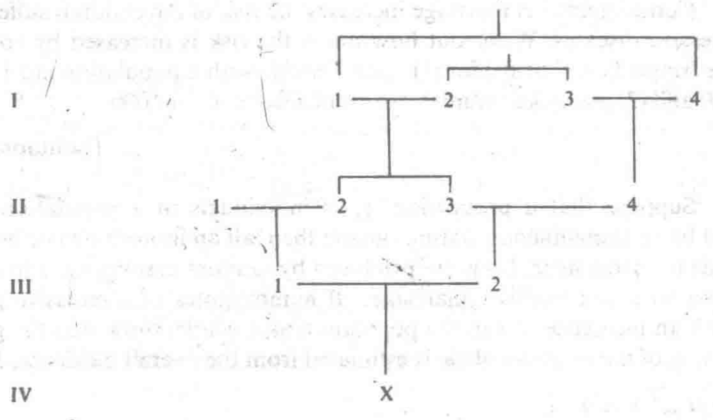
5.1 What are the inbreeding coefficients in the offspring of marriages between the following relatives? (1) single first cousins, (2) double first cousins, (3) uncle–niece.

[Solution 4]

5.2 What is the coancestry of the children of a pair of identical twins married to unrelated individuals?

[Solution 14]

5.3 The following is a human pedigree of the absence of the corpus callosum. In generation I, individuals 1 and 4 are full sibs and so are 2 and 3. In generation IV, X represents a family of eight with two affected individuals. Calculate the inbreeding coefficient of this family and that of its parent, III 2.



Data from Shapira, Y. & Cohen, T. (1973) *J. Med. Genet.*, **10**, 266–9.

[Solution 24]

5.4 If a predominantly self-fertilizing plant regularly cross-pollinates with a frequency of 1 per cent, what will be the frequency of heterozygotes at a 2-allele locus with gene frequencies of 0.2 and 0.8, assuming no selection?

[Solution 34]

5.5 Suppose that a population of a predominantly self-fertilizing plant is polymorphic for two alleles, *a* and *b*, and the frequencies of the three genotypes are

aa	*ab*	*bb*
0.54	0.12	0.34

What frequency of cross-pollination does this indicate, assuming there is no selection?

[Solution 44]

5.6 What would be the inbreeding coefficient after one generation of double first-cousin mating followed by three generations of full-sib mating?

[Solution 54]

5.7 Two highly inbred lines of a plant are crossed to produce an F_1 generation. The F_1 individuals are selfed to produce an F_2. Individuals of the F_2 are then backcrossed to the F_1 and to one of the inbred lines. What are the inbreeding coefficients of the progeny of these two backcrosses?

[Solution 64]

5.8 Consanguineous marriage increases the risk of the children suffering from recessive diseases. Work out how much the risk is increased by cousin marriage (single first cousins) for (1) cystic fibrosis with a population incidence of 1/2,500 and (2) phenylketonurea with an incidence of 1/11,000.

[Solution 74]

5.9 Suppose that a proportion, *y*, of individuals in a population are produced by consanguineous matings giving them all an inbreeding coefficient of *F*, while the remainder, $1-y$, are produced by random mating, e.g. a human population with some cousin marriages. If homozygotes of a recessive gene occur with an incidence of *I* in the population as a whole, show that the gene frequency, *q*, of the recessive allele is estimated from the overall incidence, *I*, by

$$(1-yF)q^2+yFq=I$$

[Solution 84]